Near-infrared spectroscopy for the assessment of peripheral tissue oxygenation in pulmonary arterial hypertension

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May 2016

To the Editors,

On behalf of all the authors, I would like to thank you for extending us the possibility to publish our work as a Research letter in the *European Respiratory Journal.*

We also want to extend our appreciation to the editor and reviewers for taking the time and effort to provide as with valuable comments that we used to revise our manuscript. Please find a detailed response to the reviewers' comments in the manuscript files.

Sincerely,

Marios Panagiotou, MD.

Near infrared spectroscopy for the assessment of peripheral tissue oxygenation in pulmonary arterial hypertension.

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"take home" message: Near infrared spectroscopy offers a qualitative, noninvasive indication of mixed venous oxygen saturation in PAH.

Pulmonary arterial hypertension (PAH) is characterised by increased pulmonary vascular resistance and results in increased morbidity and mortality due to right heart failure and a progressive decline in cardiac output (CO) [1]. The latter disturbs oxygen delivery to the periphery and may lead to pathological changes in tissue oxygenation. The balance between global oxygen supply and demand is reflected in mixed venous oxygen saturation (SvO_2), an index that is generally reduced in patients with PAH [2]. SvO_2 at baseline is one of the strongest predictors of survival in PAH [3-5]; this is also true for changes in SvO_2 during follow-up [4]. Cut-off values of 60% [6] and 65% [4] have been used to distinguish between prognostic groups suggesting that these may be suitable treatment goals. SvO_2 is measured invasively in the pulmonary artery, where venous blood mixes after circulating through the superior and inferior vena cava, coronary sinuses and the right-heart chambers.

Spatially resolved near infrared spectroscopy (NIRS) offers a noninvasive, rapidly responsive method for measuring skeletal muscle oxygenation by examining absorption differences in the near infrared spectrum of light between oxy- and deoxy- haemoglobin and myoglobin molecules in the microvasculature. The *tissue oxygenation index* (StO_2) is commonly adopted as an index of the dynamic balance between local tissue oxygen supply (availability) and utilization (extraction) in both health and disease [7, 8]. Because the contribution of the myoglobin to the NIRS signal is not critical, StO_2 is largely considered as the ratio of oxygenated to total tissue hemoglobin concentration expressed as [oxyhemoglobin/ (oxyhemoglobin + deoxyhemoglobin)] × 100 (%). To evaluate NIRS in PAH, we correlated measurement of vastus lateralis StO_2 with SvO_2 and venous oxygen saturation in the inferior vena cava ($SivcO_2$) during right heart catheterisation.

To measure StO_2, one transcutaneous sensor (S-Type Probe; NIRO-200NX spatially resolved spectrophotometer, Hamamatsu Photonics KK, Japan) was placed over each vastus lateralis muscle, 10-12 cm above the lateral epicondyle. StO_2 values shown are the average values obtained from both legs at the time of SvO_2 and $SicvO_2$ single-point measurements. SvO_2 was measured from the distal port of the Swan–Ganz catheter. Resting SivcO2 was measured with a pigtail catheter advanced through the right internal jugular vein sheath to the level of S1 vertebra.

Concurrent, single-point measurements of SvO_2 and StO_2 were repeated during supine exercise in consecutive patients who consented to this task. One patient performed straight leg raise and nine patients exercised on an electronically braked lower limb cycle ergometer secured to the catheterization table. Subjects cycled at 60 revolutions/min for 6 minutes at a constant workload set at 50% of peak work rate achieved during an upright cycle cardiopulmonary exercise test the previous day. SvO2 and StO_2 were measured during the sixth minute. Supplementary oxygen was provided as required to maintain normoxia.

Twenty-five subjects with PAH were studied at rest, 10 of whom also exercised.
The main patient characteristics are presented in figure 1. Combining all the resting and exercise data points (n=35), StO_2 showed a good correlation with SvO2 (r=.703, p<.001). This level of correlation persisted when looking separately at rest (r=.701, p<.001) and exercise data (r=.863, p=.001) (figure 1) but also the change from rest to exercise in StO_2 and S_vO_2 (r=.669, p=.034). A significant reduction (p<.001) was observed in StO_2 during exercise. Resting values of StO_2 exhibited similar level of correlation with $SivcO_2$ (r=.655, p=.001). A good correlation (r=.703, p<.001) was observed between $SivcO_2$ and

SvO_2, whereas the resting correlations of StO_2 with S_vO_2 and $SivcO_2$ were not statistically different (Z=0.3, p =.76).

Resting StO_2 correlated with age (r=-.416, p= .038) but also with indices of disease severity including the six-minute walk distance (r=.528, p=.008), N-terminal pro-brain natriuretic peptide (r=-.395, p=.05) and diffusing lung capacity for carbon monoxide percent predicted (r=.398, p=.049).

To our knowledge, this is the first study to report on the association between StO_2 and SvO_2. Good correlation between vastus lateralis StO_2 and femoral venous oxygen saturation has also been reported in healthy trained subjects [9] albeit earlier studies did not confirm such correlation [10, 11]. However, comparisons should be made with caution as responses of StO_2 depend highly on the mode, intensity and duration of exercise and neither of those studies is matched in design to our resting and steady-state exercise protocol. Instead, they report on measurements either during incremental exercise [9] or over time during constant load exercise [10, 11].

Nonetheless, the correlation between StO_2 and SvO_2 or $SivcO_2$ is not absolute and results of relating StO_2 to venous blood oxygenation should not be interpreted in a quantitative sense. This may be because the specific tissue volume investigated by NIRS is not fully representative of the oxygen status of the body segment (lower limb) or global tissue oxygenation as measured by $SivcO_2$ and SvO_2, respectively [7]. It is not surprising that the highest correlations between StO_2 and venous oxygen saturation were shown when

the sampled venous effluent was specific for the interrogated tissue volume such as that obtained from a deep forearm vein that drained the exercising muscle (r=.92) [8] or from a vein that drained only the electrically simulated muscle of dogs (r=.97) [12]. Accordingly, $SivcO_2$ would be expected to exhibit a higher correlation with StO_2 than SvO_2. However, we observed similar correlation between StO_2 and SvO_2. This seeming paradox may be due to venous return from the lower limbs being the major determinant of SvO_2 in the supine leg exercise.

The design of the present study does not allow for reliable conclusions on the tissue oxygen status *per se*; the presented measurements should be interpreted within the context of oxygen supplementation to maintain resting normoxia and the absence of a matched control group. However, our findings provide support for the use of NIRS in the investigation of the pathophysiological abnormalities in PAH. Also, taken together, findings cannot exclude a role of the periphery in the pathophysiology of PAH since skeletal muscle tissue microenvironment, an important factor of the local oxygen status, is disturbed in PAH [13]. Perhaps, combination of NIRS with other techniques such as vascular occlusion, sidestream dark field imaging and histological examination could enable further exploration.

Limited experience from application of NIRS in PAH showed significantly lower resting thenar muscle oxygen saturation in PAH patients compared with matched healthy subjects and patients with CHF [14]. Also, study of the kinetics of the vastus lateralis fractional oxygen extraction (% Δ deoxyhemoglobin/myoglobin) relative to oxygen uptake at the beginning of heavy-intensity exercise, suggests that patients with PAH have

greater microvascular oxygen delivery-to-utilization inequalities compared to healthy control, which contribute to slow adaptation rate of aerobic metabolism [15].

In summary, skeletal muscle StO_2 in PAH subjects correlated significantly with SvO_2 under both resting and exercise conditions. Also, StO_2 correlated significantly, albeit weakly, with indices of disease severity. These novel findings suggest that StO_2 may serve as a clinical and research tool for the qualitative, noninvasive assessment of the dynamic balance between oxygen supply and utilization in PAH. Further studies are warranted to explore the value of NIRS in the assessment and prognosis of PAH.

Figure legends

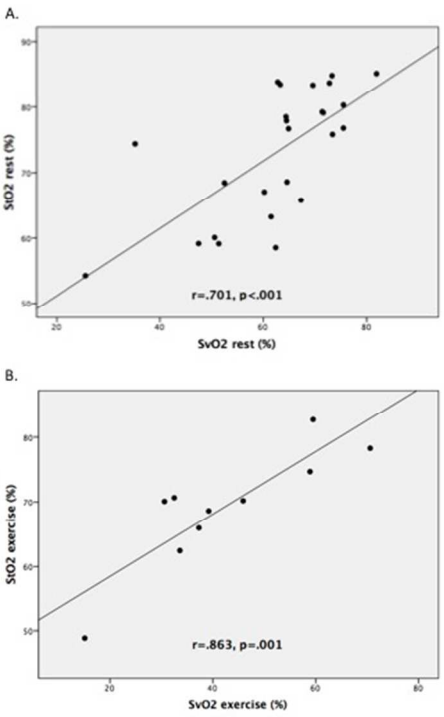
Figure 1: Patient characteristics and correlations between StO_2 and SvO_2 at rest (A) and during exercise (B).

References

1. Authors/Task Force M, Galie N, Humbert M, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J* 2016; 37:67-119.
2. Kielstein JT, Bode-Boger SM, Hesse G, et al. Asymmetrical dimethylarginine in idiopathic pulmonary arterial hypertension. *Arterioscler Thromb Vasc Biol* 2005; 25: 1414-1418.
3. Sandoval J, Bauerle O, Palomar A, et al. Survival in primary pulmonary hypertension. Validation of a prognostic equation. *Circulation* 1994; 89: 1733-1744.
4. Nickel N, Golpon H, Greer M, et al. The prognostic impact of follow-up assessments in patients with idiopathic pulmonary arterial hypertension. *Eur Respir J* 2012; 39: 589-596.
5. Wensel R, Opitz CF, Anker SD, et al. Assessment of survival in patients with primary pulmonary hypertension: importance of cardiopulmonary exercise testing. *Circulation* 2002; 106: 319-324.
6. Higenbottam T, Butt AY, McMahon A, et al. Long-term intravenous prostaglandin (epoprostenol or iloprost) for treatment of severe pulmonary hypertension. *Heart* 1998; 80: 151-155.
7. Boushel R, Langberg H, Olesen J, et al. Monitoring tissue oxygen availability with near infrared spectroscopy (NIRS) in health and disease. *Scand J Med Sci Sports* 2001; 11: 213-222.
8. Mancini DM, Bolinger L, Li H, et al. Validation of near-infrared spectroscopy in humans. *J Appl Physiol (1985)* 1994; 77: 2740-2747.
9. Vogiatzis I, Habazettl H, Louvaris Z, et al. A method for assessing heterogeneity of blood flow and metabolism in exercising normal human muscle by near-infrared spectroscopy. *J Appl Physiol (1985)* 2015; 118: 783-793.
10. Costes F, Barthelemy JC, Feasson L, et al. Comparison of muscle near-infrared spectroscopy and femoral blood gases during steady-state exercise in humans. *J Appl Physiol (1985)* 1996; 80: 1345-1350.
11. MacDonald MJ, Tarnopolsky MA, Green HJ, et al. Comparison of femoral blood gases and muscle near-infrared spectroscopy at exercise onset in humans. *J Appl Physiol (1985)* 1999; 86: 687-693.
12. Wilson JR, Mancini DM, McCully K, et al. Noninvasive detection of skeletal muscle underperfusion with near-infrared spectroscopy in patients with heart failure. *Circulation* 1989; 80: 1668-1674.

13. Panagiotou M, Peacock AJ, Johnson MK. Respiratory and limb muscle dysfunction in pulmonary arterial hypertension: a role for exercise training? *Pulm Circ* 2015; 5: 424-434.
14. Dimopoulos S, Tzanis G, Manetos C, et al. Peripheral muscle microcirculatory alterations in patients with pulmonary arterial hypertension: a pilot study. *Respir Care* 2013; 58: 2134-2141.
15. Barbosa PB, Ferreira EM, Arakaki JS, et al. Kinetics of skeletal muscle O2 delivery and utilization at the onset of heavy-intensity exercise in pulmonary arterial hypertension. *Eur J Appl Physiol* 2011; 111: 1851-1861.

Patient characteristic	Rest (n=25)	Exercise (n=10; rest/exercise)
Age, y	61.9 ± 11.6	55.6 ± 8.4
Sex, male: female	11: 14	4: 6
IPAH; FPAH; CTD; CHD; PoPH	13;1;7;1;3	4;1;3;1;1
6MWD, m	256 ± 134	344 ± 144
NTproBNP, pg/ml	1101 (153, 2928)	263 (42, 1461)
mPAP, mm Hg	43 ± 11	40.7 ± 10.2/66.1 ± 13.8*
CO, L/min	4.6 ± 1.7	5.5 ± 1.96/8.6 ± 3.3*
PVR, Wood units	9.5 ± 5.9	7.3 ± 4.3/7.9 ± 4.5
SvO_2, %	62.5 ± 12.9	70.3 ± 8.6/42.3 ± 16.6*
$SivcO_2$, %	64.2 ± 14.3	N/A
StO_2, %	73.1 ± 9.8	77.62 ± 6.9/69.2 ± 9.2*



Data are presented as mean ± SD or median and quartiles. 6MWD: six-minute walk distance; IPAH: idiopathic pulmonary arterial hypertension; FPAH: familial pulmonary arterial hypertension; CTD: connective tissue disease-associated PAH; CHD: congenital heart disease-associated pulmonary arterial hypertension; PoPH: portopulmonary arterial hypertension; mPAP: mean pulmonary artery pressure; CO: cardiac output; PVR: pulmonary vascular resistance; SvO2: mixed venous oxygen saturation; SivcO2: inferior vena cava oxygen saturation; StO2: quadriceps tissue oxygen saturation. * Statistically significant difference between values at rest and during exercise, p<0.01.

Legend: Figure 1: Patient characteristics and correlations between StO2 and SvO2 at rest (A) and during exercise (B).
254x190mm (72 x 72 DPI)

ERJ-00608-2016

" Near infrared spectroscopy for the assessment of peripheral tissue oxygenation in pulmonary arterial hypertension."

Responses to Editors' and reviewers' comments

Reviewer: 1

1. Although these results in a small group seem clinically important, I would like to see the sensitivity and specificity of StO2 according to the prognostic relevant cut of SvO2 values of 60% and or 64% as mentioned by the authors in the introduction.

Response: We appreciate this comment. However, the limited available space of the Research letter does not allow further elaboration.

2. Ad 1. This lines can be shown in the graphs from Figure 1.as well.

Response: We regret we are unable to understand this comment.

3. Figure 1. I would prefer only Figure B (rest) and C (exercise) separately. This is also statistically more sound. Only one data point for each measured subject in one correlation graph.

Response: The recommendation has been applied in the new figure.

4. From the tables 1 and 2. From the SD values (NTproBNP, CO (exercise SD= 10,9??, typing error?) and SvO2 it seems that the data is not normally distributed and therefore the variance should be given as a range instead of SD

Response: NTproBNP is now presented as median and quartiles and the typing error has been corrected. The rest of the values are normally distributed.

5. Table 3 shows only the correlations of resting StO2, I would expect also a correlation between StO2 during exercise and 6MWD (although n=10), please show these values

Response: We did not observe a correlation between StO2 during exercise and 6MWD.

Reviewer: 2

Comments to the Author

1. *It is mentioned that "The exercised subjects showed a significant reduction in StO2 during exercise (p<.001)". Is this "abnormal"? As the author recognize, lack of a control group make it difficult to grasp a consistent view on what this measurement actually tell us.*

Response: We agree that in the absence of a control group we cannot draw any safe conclusion. We have now understated this finding and simply report it in the Results paragraph to demonstrate sensitivity of the NIRS method in peaking up changes in oxygenation during exercise.

2. *StO2 interrogates the lower limbs. Thus, better correlations with inferior cava SO2 (compared to SvO2) could be anticipated. This, however, was not the case. This reviewer found it hard to logically conciliate this apparent paradox.*

Response: This appear paradoxical at first sight. However, seen from a different perspective, this suggests that the venous return from (or the oxygenation status of) lower limb is the major determinant of SvO2 in the supine exercise. We have added this comment in the text.

3. *Correlations were found between resting (not exercise) StO2 with six-minute walk distance (6MWD) (r=.528, p=.008) less consistently with NTproBNP (r=-.395, p=.05), DLCO% pred. (r=.398, p=.049) and age (r=-.416, p= .038). They are not particularly impressive and the small number of observations and several confounders make them difficult to interpret.*

Response: We have understated these observations.

4. Absolute StO2-NIRS is likely to be strongly dependent on the work rate performed. Subjects cycled at 50% of their peak work rate. Thus, less impaired patients likely exercised at higher work rates. Inter-subject variations in StO2 might reflect this rather than true physiological impairment.

Response: We agree on the validity of this comment but cannot be applied in the Research letter.

5. I am really not sure if the resting correlation (StO2 x SvO2) would remain significant if the single subject on the far left were excluded.

Response: The correlation at rest remains significant after removing the subject on the far left: r=.602, p=.002

6. The authors mention that "This finding extends previous experience from application of NIRS in PAH (limited to a single study), showing significantly lower resting thenar muscle oxygen saturation in PAH patients compared with matched healthy subjects but also, patients with CHF [29]." A quick search on PUBMED revealed a study for Brabosa et al. (Eur J Appl Physiol. 2011 111(8):1851-61) in PAH using similar methodology. The reviewer had no access to this paper but, based on the Abstract, it seems to address a similar topic in PAH.

Response: The study by Barbosa et al. is now cited in the Research letter.

6. Was there any correlation with SaO2? Cardiac output (CO)? DO2 (CO x CaO2?)

Response: We did not perform measurement of SaO2.

7. Due to the cross-sectional nature of the study, it remains unclear whether NIRS would be sensitive enough to detect positive "peripheral" consequences of improved central hemodynamics.

Response: We appreciate the concern of this reviewer. However, this is not apllicable to the Research letter.